Original articles

J. Perinat. Med.
5 (1977) 172

Hemoglobin changes during pregnancy and growth disturbances in the neonate

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The extent to which anemias of pregnancy affect length of gestation and fetal growth varies among the many reports [1, 2, 6, 11, 12, 18, 22]. Because the hemoglobin (Hb) normally decreases during pregnancy, results obtained at varying times during pregnancy (e.g. during the first or the third trimester) are not comparable. Investigations about the role of the relative changes of hemoglobin during pregnancy have not been done. This study pursues that question from the data of the prospective Study on Pregnancy and Child Development of the Germany Research Council (Deutsche Forschungsgemeinschaft).

Material and Methods

Study patients entered the study during the first trimester and were examined throughout the pregnancy at four week intervals. Details of birth and infant outcome were accurately documented. All data were centrally collected and evaluated. Details of this study have been described by KOLLER [10]. Hemoglobin values of 4690 women were determined in the first trimester upon admission to the study and agein in the third trimester (especially at the middle of the third trimester). Thus, individual changes could be assessed. Multiple births were excluded from the analysis.

The method of hemoglobin determination varied among the 18 collaborating obstetric departments; thus, standardization and determination of the standard error could not be accomplished. Since there should be no correlation between the method of hemoglobin determination and the frequency of fetal growth disturbances, the heterogeneity of the assay methods did not influence the conclusions.

The two variables examined were the length of gestation and the incidence of hypotrophic newborns. This included all infants with a birth weight below the tenth percentile recording to MAU [13]. About 2/3 of these newborns weighed less than 2500 grams and 1/3 weighed more than 2500 grams.

Multiple regression analyses yielded information on the variation of specific measurements from the

Curriculum vitae

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general maturation state of the infant. Thus, it was possible to assess whether an infant was shorter or longer in relation to his weight, head circumference, gestational age or clinical maturity. Statistical analysis used the Chi-square test.

Results

Pregnant women who had initially low hemoglobin values were often given iron and vitamin preparation. Thus, they correspondingly more often showed an increase in hemoglobin than those with intermediate or higher initial values. The increase was generally up to 2 g%, so that by the third trimester the values were still not very high. (Tab. I). If a hemoglobin value at the first examination was in the intermediate or upper range there was in 86.4 % of the cases a decrease in the hemoglobin, coincident with the hemodilution during pregnancy. (Tab. I).

If the hemoglobin at the first examination was less than 11.2 g%, the incidence of prematurity was only slightly higher than with intermediate hemoglobin. Similarly, there were only slightly more hypotrophic infants from anemic mothers. (Tab. II). The other indicators of maturity showed equally few unequivocal deviations in the presence of maternal anemia in the first trimester (see below).

The search for correlation between hemoglobin values in the third trimester and growth disturbances had surprisingly different results. **Pregnant women with a high hemoglobin content gave birth to prematures and dystrophic infants far more frequently than expected.** (Tab. III). Simultaneously, the number of infants who weighed less, were too short and had too large head circumferences in correlation to the corresponding other parameters was increased. With a hemoglobin over 14.5 g% in the third trimester, 11.2 % of the infants weighed less than 2500 grams and 25.8 % weighed less than 2750 grams.

An analysis of these correlations with the first trimester hemoglobin values showed that **not the women with the initial low values and a later increase were affected, but those with the initial intermediate and higher values whose hemoglobin levels had not or only slightly decreased, i.e. those in whom the physiological hemodilution of the pregnancy had not occurred.** (Tab. IV).

These results were independent of parity, age, weight and socio-economic status of the patient. A correlation of the findings with toxemia was attempted and patients were classified as hypotensive, normotensive and hypertensive. The above described correlation was found in the hypertensive and normotensive patients, while patients with blood pressures above 150 mm Hg had a notably increased incidence of both prematures and dysmatures with low hemoglobin values in the third trimester.

Tab. I. Cases with Hb changes (% of N): Hemoglobin values in the first trimester and changes in hemoglobin throughout the pregnancy (to the third trimester).

Hb in 1st trimester (g%)	Increased by > 2 g%	Increased by < 2 g%	Decreased by < 2 g%	Decreased by > 2 g%	N
< 11.2	15.5	52.9	30.5	1.1	387
12.3 – 12.8	2.8	31.3	61.1	4.8	1694
12.9 – 15.2	0.7	12.9	62.8	23.6	2398
> 15.2	0.5	2.4	20.8	76.3	211

Tab. II. Hypotrophic newborns: Incidence of dysmature newborns (birth weight < 10 th percentile) and hemoglobin value in the first trimester. $X^2 = 1.2$ (n.s.).

Hb in 1st trimester (g/)	%	N
< 11.2	10.8	387
11.3 – 12.8	9.3	1694
12.9 – 15.2	9.5	2398
> 15.2	9.0	211

Tab. III. Incidence of hypotrophic (weight < 10th percentile) and premature infants (gestational duration < 260 days) in relation to third trimester hemoglobin values.

Hb in 3rd trimester (g%)	Hypotrophic*	Prematures	N
< 10.4	7.8	6.0	490
10.5 – 12.8	8.8	7.1	3205
12.9 – 14.4	12.0	10.5	860
> 14.4	15.6	16.2	135

* $X^2 = 15.9$; $p < 1\%$

** $X^2 = 26.6$; $p < 1\%$

Tab. IV. Incidence of hypotrophic newborns (weight < 10th percentile) correlated with hemoglobin value in the first trimester (< 11.2 and > 12.9 g%) and hemoglobin changes to the third trimester.

Hb in 1st trimester (g%)	Hb changes to 3rd trimester	Hypotrophic (%)	N
< 11.2	increase > 2 g%	8.2	61
	increase < 2 g%	12.0	204
	decrease < 2 g%	11.7	118
	decrease > 2 g%	–	4
> 12.9	increase > 2 g%	(5.5)	18
	increase < 2 g%	17.4	306
	decrease < 2 g%	9.2	1554
	decrease > 2 g%	6.7	731

The described correlation between first trimester anemia and the occurence of dysmaturity must take into consideration these findings. Table 4 shows that women with a low first trimester hemoglobin and only a minimal increase have more frequently hypotrophic newborn infants with 12 % and 11.7 % respectively than those with higher initial values in whom the hemodilution of pregnancy has occurred (6.7 %). The poor outcome in women lacking the decrease in hemoglobin raises the mean for the group to that of the patients with a first trimester anemia.

Discussion

Even though these findings may appear slightly confusing the pathogenetic principle becomes recognizable if some already known facts are taken into consideration.

It is known that the plasma volume increases by about 15 % more than the total amount of hemoglobin. This difference results in a hemodilution with a relative decrease in hemoglobin as expressed in Hb g%. This decrease occurs generally between the 25th and 36th gestational week and a prenatal hemoglobin of 12 g% is considered optimal. A failure of the hemoglobin to fall during pregnancy may thus indicate a relatively too low increase in plasma volume or a too large increase in hemoglobin. A high hemoglobin value leads necessarily to an increase in blood viscosity. RÄIHÄ et al [14, 15, 16], UNNERUS et al [3, 20] and BISHOP [5] have shown years ago that there is a correlation between the cardiac volume of the mother and the incidence of prematurity. These results have been criticized for methodical reasons because the values were not corrected for the maternal body size [2, 8, 17, 19], however, body weight and size of the mother are correlated with the birth weight of the child as well as with the maternal cardiac volume. HYTTEN and PAINTIN [9] showed that even if body size is taken into consideration, the incidence of low birth weight infants increases with low plasma volume.

In these studies a low cardiac volume was interpreted primarily as an indication of decreased physical capacity. As a consequence in Helsinki the so-called cardiac volume program was initiated where women with low cardiac volumes were asked to avoid physical stress. This study meanwhile comprises 50,000 cases [21] and shows that primarily those women are at risk who do not show an increase of the cardiac volume during pregnancy, i.e. a lack or insufficient increase in plasma volume. It is possible that our results of the two hemoglobin determination assess the same phenomenon. **Therefore, it maybe hypothesized that a lack of hemodilution with high initial hemoglobin values leads to fetal risk.**

This risk is seen especially in the increase of hypotrophic newborns. The multivariant analysis of the other indicators of maturity shows in addition that fatty tissue is reduced and that the infants have a relatively large head circumference in comparison to weight and length and thus resemble a genuine intrauterine growth retardation. The placentas are in part small but mature according to the criteria of BECKER [4]. It is difficult to assess the effect on the length of gestation because an increased duration of pregnancy leads normally to a decrease of hemoglobin and thus a premature delivery encounters higher hemoglobin values. Even though this influence and the variable examined cannot easily be separated, **the results point towards an increased incidence of premature infants in women with lack of hemoglobin decrease.** Our investigations leave unclarified which subordinate factor is the cause, e.g. whether it is a relative high viscosity of the blood or whether

other factors such as disturbances in blood distribution and placental perfusion play a role or whether there are compensatory processes with a relatively too large increase of the total hemoglobin.

In summary, two risk groups can be identified:

1. **women with initially low hemoglobin values and a failure to increase them.**
2. **women with higher initial values and a lack of decrease.**

If our results should prove to be reproducible with adequate controls the easily followed variable hemoglobin should allow the proper identification of these women at risk.

Summary

From the material of the prospective Study on Pregnancy and Fetal Development we examined the influences of changes in hemoglobin during pregnancy on gestational duration and fetal growth.

At least two hemoglobin determinations in 4690 women were carried out.

86.4% of all women with initial hemoglobin above 11.2 g% had a decrease in hemoglobin as an indication of a physiological plasma volume increase. Women with low values (less than 11.2 g%) showed an increase in 15.5%.

If the hemoglobin during the first trimester was less than 11.2 g% the incidence of prematures and hypotrophic infants (birth weight below the 10th percentile) was only slightly increased. However, women with a high hemoglobin value in the third trimester has significantly more premature and dysmature births (16.2 and 15.6%). Multivariant analysis of all signs of maturity showed that those who weighed relatively low were particularly those with low body weight, relatively low length and a large head circumference in relation to their weight. The placentae were small but mature. The analysis of the correlation with the first trimester hemoglobin values demonstrated that particularly women with intermediate and high values during the first trimester and whose hemoglobin during the pregnancy had not or only insignificantly dropped were affected, i.e. those in whom the physiological dilutional anemia of pregnancy had not occurred. These findings were independent of age, parity, weight, socio-economic status and presence or absence of toxemia. A comparison of both hemoglobin values showed that of the women with a normal decrease of hemoglobin during pregnancy those with lower initial values had more prematures and dysmatures than those with normal hemoglobin values in the first trimester.

This allows the **identification of two risk groups: (1) pregnant women with initially low values without subsequent increase of hemoglobin**; and **(2) pregnant women with initially high values with a failure of the physiological decrease of hemoglobin to occur.** Whether the second group represents a lack of hemodilution or other mechanisms is unclear. These findings are supported by the results of the Finnish authors (RÄIHÄ and UNNERUS) who also found an increased incidence of prematurity and dysmaturity in women with a low cardiac volume and a lack of increase in cardiac volume during pregnancy.

Keywords: Fetal growth disturbance, hemoglobin, plasma volume, prematurity.

Zusammenfassung

Veränderung des Hämoglobins während der Schwangerschaft und Reifestörung des Neugeborenen

Anhand des Materials der prospektiven Studie „Schwangerschaftsverlauf und Kindesentwicklung" wurde untersucht, welche Auswirkungen Veränderungen des Hämoglobins (Hb) im Verlaufe der Schwangerschaft auf die Tragzeit und das fetale Wachstum haben. **Insgesamt wurden 4690 Frauen untersucht, bei denen mindestens 2 Hb-Bestimmungen während der Gravidität durchgeführt worden waren.**

86,4 % aller Frauen mit einem Anfangs-Hb über 11,2 g% zeigten als Zeichen einer physiologischen Plasmavolumenvermehrung einen Abfall ihres Hb. Schwangere mit niedrigen Werten (= 11,2 g%) wiesen häufiger auch einen Anstieg (15,5%) auf.

Lag das Hb bei der ersten Untersuchung (im 1. Trimenon) unter 11,2 g%, war die Frequenz Frühgeborener und hypotropher Kinder (Gewicht unter der 10. Perzentile) nur gering erhöht. Ein völlig anderes Bild entstand, wenn man die Hb-Werte des 3. Trimenons zugrunde legte. **Schwangere mit einem hohen Hb-Gehalt im 3. Trimester brachten weit über zufällig häufig Früh- und Mangelgeborene zur Welt** (16,2 bzw. 15,6%). Die multivariante Analyse aller Reifeparameter zeigte, daß es sich bei den relativ untergewich-

tigen Kindern vor allem um solche mit geringer Körpermasse, relativ kleiner Länge und im Verhältnis zu ihrem Gewicht relativ großem Kopf handelte. Die Plazenten waren klein, aber reif. Analysierte man diese Zusammenhänge unter der Bedingung der Hb-Ausgangswerte des 1. Trimenon, so zeigte sich, daß vor allem Schwangere mit mittleren und höheren Werten bei der ersten Untersuchung betroffen waren, deren Hb-Gehalt im Verlaufe der Schwangerschaft nicht oder nur unwesentlich gesunken war, bei denen also die physiologische Schwangerschaftshydrämie nicht eingetreten war. Diese Befunde waren unabhängig vom Alter, von der Parität, dem Gewicht, dem Sozialstatus und einer evtl. vorhandenen EPH-Gestose der Schwangeren.
Unter Berücksichtigung beider Hb-Werte zeigte sich weiter, daß in der Gruppe der Frauen mit einem normalen Abfall des Hb während der Schwangerschaft diejenigen mit niedrigen Anfangs-Hb-Werten häufiger früh- und mangelgeborene Kinder zur Welt brachten als solche mit normalen Hb-Werten im 1. Trimenon.
Es können somit 2 **Risikogruppen** unterschieden werden:

1. **Schwangere mit anfänglich niedrigen Hb-Werten ohne Anstieg des Hb,**
2. **Schwangere mit anfänglich hohen Hb-Werten bei denen der physiologische Abfall der Hb-Werte ausbleibt.**

Ob bei der zweiten Gruppe eine mangelnde Hämodilutation oder andere Mechanismen eine Rolle spielen, bleibt unklar. Diese Befunde finden ihre Unterstützung in Ergebnissen von finnischen Autoren (RÄIHÄ und UNNERUS) die bei Frauen mit einem kleinen Herzvolumens während der Schwangerschaft ebenfalls vermehrt Früh- und Mangelgeborene gesehen haben.

Schlüsselworte: Fetale Hypotrophie, Frühgeburt, Hämoglobin, Plasmavolumen

Résumé

Altération de l'hémoglobine en cours de grossesse et perturbation de la maturation du nouveau-né
Nous aidant du matériel de l'étude prospective sur le déroulement de la grossesse et le développement de l'enfant, nous avons examiné les conséquences que peuvent avoir des altérations de l'hémoglobine (Hb) en cours de grossesse sur la durée de la gravidité et la croissance foetale. A cet effet **nous avons observé 4690 femmes chez lesquelles nous avons effectué au moins deux analyses de Hb durant la grossesse.**
86,4% de toutes les femmes avec une première Hb supérieure à 11,2% ont enregistré par la suite une baisse de leur Hb, signe d'une augmentation physiologique du volume du plasma. Par contre, chez les femmes enceintes ayant des valeurs basses (= 11,2%) au départ, on a observé plus fréquemment une hausse de l'hémoglobine (15,5%).
Pour une hémoglobine inférieure á 11,2! au premier examen (premier trimestre), on n'observa qu'une très légère hausse de la fréquence des prématurés et des enfants hypotrophes (poids inférieur au 10 pour cent requis). Le tableau est tout différent si on considère les résultats du troisième trimestre: **les femmes enceintes ayant un taux de'Hb élevé à cette période ont mis au monde une moyenne anormalement plus grande de bébés prématurés ou non sains** (16,2 et 15,6%). L'analyse multiple de tous les paramètres de maturité a montré qu'il s'agissait chez les enfants au poids relativement inférieur à la normale surtout de bébés plus menus et petits avec une téte proportionnellement grosse. Les placentas étaient réduits, mais métures. Comparant ces proportions aux valeurs Hb du premier trimestre, on s'est aperçu qu'il s'agissait là surtout des patientes dont les taux de Hb s'étaient révélés moyens ou élevés à la première analyse, mais n'avaient pas ou que peu baissé au cours de la grossesse, c.à.d. les femmes où n'était apparue aucune hydrémie physiologique de gravidité. Ces résultats ne dépendent nullement de l'âge, de la parité, du poids, du statut social ni d'une gestose EPH éventuelle.
Compte tenu des deux valeurs Hb, on a observé par la suite que dans le groupe des femmes dont l'hémoglobine a baissé normalement en cours de grossesse, celles qui ont eu au départ des taux de Hb peu élevés ont mis plus souvent au monde des bébés prématurés ou mal formés que celles ayant enregistré des valeurs normales de Hb au premier trimestre.
Ceci permet donc de distinguer **deux groupes «à risque»:**

1. **Femmes enceintes avec premiers taux de Hb bas sans hausse ultérieure;**
2. **femmes enceintes avec, au départ, des taux de Hb élevés et chez lesquelles n'apparaît pas la baisse physiologique des valeurs de Hb.**

On ne sait pas encore ce qui joue un rôle chez le deuxième groupe: l'absence d'hémodilution ou d'autres mécanismes. Ces résultats confirment les études d'auteurs finlandais (RÄIHÄ et UNNERUS) qui avaient également constaté une augmentation des bébés prématurés et non sains chez les femmes ayant un petit volume cardiaque, ou dont le volume cardiaque n'a pas augmenté en cours de grossesse.

Mots-clés: Hémoglobine, hypotrophie foetale, naissance prématurée, volumes de plasma.

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Received November 24, 1976. Accepted March 1, 1977.

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